PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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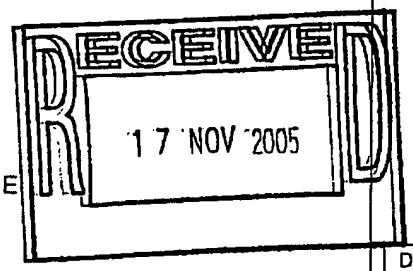

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.11.2005
Applicant's or agent's file reference: PBD00032 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003082	02.09.2004	02.09.2003

Applicant: PROSIDION LTD

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Lafitte-de Jong, S Tel. +31 70 340-4827

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PBD00032 PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/003082	International filing date *(day/month/year)* 02.09.2004	Priority date *(day/month/year)* 02.09.2003
International Patent Classification (IPC) or national classification and IPC A61K31/40, A61K31/426, A61K45/06, A61P3/10		
Applicant PROSIDION LTD		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.09.2005	16.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Leherte, C Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/003082

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-43	as originally filed
Claims, Numbers	
1-26	as originally filed
Drawings, Sheets	
1/6-6/6	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-25 (all partially),1, 2, 5, 6, 8-21 (with respect to industrual applivability)

because:

☒ the said international application, or the said claims Nos. 1, 2, 5, 6, 8-21 (with respect to industrual applivability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-25 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-26 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-12, 15, 16, 20-26
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Re Item III.
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 1, 2, 5, 6 and 8-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2) Claims 1-12, 18 and 23-25 encompass a genus of compounds defined only by their function ("antidiabetic", "alpha glucosidase inhibitor", "biguanide", "insulin secretagogue", "insulin sensitiser" and "PPARγ agonist insulin sensitiser"), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.
The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.
The claims cover all combinations of glutaminyl thiazolidine or glutaminyl pyrrolidine and another antidiabetic agent, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such combinations.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

3) Present claims 5-7 and 9-22 relate to an extremely large number of disease states. In fact, the expression "condition associated with diabetes mellitus, the prediabetic state and/or obesity" does not allow any practical application in the form of a defined, real treatment of a pathological condition. A lack of clarity (and/or conciseness) within the

meaning of Art. 6 PCT therefore arises.
Independent of the above, the Applicant has not provided any test to demonstrate whether a disease is associated with diabetes mellitus, the prediabetic state and/or obesity. There is therefore insufficient disclosure (Art. 5 PCT) to allow the skilled man to determine which diseases fall within the definition.

4) Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the pharmaceutical combinations, containing glutaminyl thiazolidine or glutaminyl pyrrolidine with another antidiabetic agent, selected from among the ones explicitly disclosed in claims 13, 15, 17 or 19, for the treatment of the diseases explicitly mentioned in the claims.

No opinion of the present Authority will be given in respect of subject-matter which IS not covered by the search report (Rule 66.1(e) PCT).

Re Item IV.
Lack of unity of invention

The separate inventions/groups of inventions are:

1-12, 23-25 (all partially), 13, 14
A method or pharmaceutical composition for glycaemic control in a mammal, comprising the administration of glutaminyl thiazolidine or glutaminyl pyrrolidine, or a pharmaceutically acceptable salt thereof, and an alpha glucosidase inhibitor.
1-12, 23-25, (all partially), 15, 16, 20-22, 26
A method or pharmaceutical composition for glycaemic control in a mammal, comprising the administration of glutaminyl thiazolidine or glutaminyl pyrrolidine, or a pharmaceutically acceptable salt thereof, and a biguanide.
1-12, 23-25, (all partially), 17
A method or pharmaceutical composition for glycaemic control in a mammal, comprising the administration of glutaminyl thiazolidine or glutaminyl pyrrolidine, or a pharmaceutically acceptable salt thereof, and an insulin secretagogue.
1-12, 23-25, (all partially), 18, 19
A method or pharmaceutical composition for glycaemic control in a mammal, comprising

the administration of glutaminyl thiazolidine or glutaminyl pyrrolidine, or a pharmaceutically acceptable salt thereof, and an insulin sensitizer.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

According to Rule 13.1 PCT, "The International application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept". This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".
Rule 13.1-2 PCT requires that claimed alternatives are of a similar nature in having a common property or activity, and either a significant structural element shared by all of the alternatives, or in case a common structure is absent, all alternatives belonging to a recognized class of chemical compounds in the art to which the invention pertains [compare "Administrative Instructions under the PCT", Annex B, Unity of Invention, paragraph (f)].
The problem underlying the present application as it is defined in the claims and the description is to provide a method or pharmaceutical composition for glycaemic control, in particular for the treatment of diabetes mellitus in a mammal.
The proposed solution is the administration of a combination comprising glutaminyl thiazolidine or glutaminyl pyrrolidine, or a pharmaceutically acceptable salt thereof, and another diabetic agent.
US6548481 discloses compositions containing glutaminyl thiazolidine or glutaminyl pyrrolidine salts and additionally comprising an active ingredient having hypoglycaemic action selected from the group consisting of biguanide metformin, sulphonylureas, saccharides and thiazolidinediones.
The idea of using the presently proposed combination to overcome the problem identified above is therefore not novel, Consequently it can not serve as a single general inventive concept linking the various inventions given in the present application, which are mere alternatives for the combinations of the prior art.
Alpha glucosidase inhibitors, biguanides, insulin secretagogues and insulin sensitisers

share the common property of being antidiabetic agents, but they do not share a significant structural element, nor do they belong to a single recognized class of chemical compounds in the art to which the invention pertains: In fact, each of these individual groups form themselves distinct individual recognized classes of chemical compounds in the pharmacological art. There is no expectation from the knowledge in the art that members of all these classes will behave in the same way in the context of the claimed inventions. There is also no expectation in the art that each member of each of these classes can be substituted one for the other, with the expectation that the same intended result would be achieved.
In the present application no further technical features can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different inventions listed above.

Re Item V.
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International Search Report has been drawn up (i.e. only for pharmaceutical compositions, containing glutaminyl thiazolidine or glutaminyl pyrrolidine and another antidiabetic agent, selected from the ones explicitly disclosed in the claims, for the treatment of the diseases explicitly mentioned in the claims).

1) DOCUMENTS USED IN EXAMINATION

The following documents are referred to in this communication:

D1: US-B1-6 548 481 (DEMUTH HANS-ULRICH ET AL) 15 April 2003 (2003-04-15)
D2: US 2003/119736 A1 (DEMUTH HANS-ULRICH ET AL) 26 June 2003 (2003-06-26)
D3: US 2003/162820 A1 (DEMUTH HANS-ULRICH ET AL) 28 August 2003 (2003-

08-28)

D4: GOODMAN G A ET AL: "GOODMAN and GILMAN'S The Pharmacological Basis of Therapeutics , (alpha-glucosidase inhibitors)" 2001, PAGE(S) 1701-1707 sulphonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

2) LACK OF NOVELTY

The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 1-12, 15, 16 and 20-26 is not new.
Document D1 discloses compounds analogous to dipeptide compounds that are formed from an amino acid (that can be glutamine) and a thiazolidine or pyrrolidine group, and salts thereof, and to the use of these compounds in the treatment of impaired glucose tolerance, glycosuria, hyperlipidaemia, metabolic acidoses, diabetes mellitus, diabetic neuropathy and nephropathy, and that, since the anti-hyperglycaemic action of those compounds is exhibited independently of other known oral anti-diabetics, they are analogously suitable for use in combination therapies with biguanides (metformin), sulphonylureas, saccharides and thiazolidinediones.

3) INVENTIVE STEP

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-26, as far as novel, does not involve an inventive step.

The problem to be solved by the present application is the provision of a medicament for the treatment of diabetes.

The solution proposed by the applicant is a medicament containing glutaminyl thiazolidine or glutaminyl pyrrolidine and another antidiabetic agent.

Documents D2 and D3 disclose the use of glutaminyl thiazolidine or glutaminyl pyrrolidine for the treatment of diabetes.

Document D4 describes the use of alpha glucosidase inhibitors, biguanides, insulin secretagogue and insulin sensitiser for the treatment of diabetes and their use with other antidiabetic agents.

Document D1 states that in order to intensify the blood-sugar-reducing action of various anti-diabetics, use is frequently made of combinations of different orally effective anti-diabetics.

Therefore the features disclosed in D2 or D3, and D4 would be (in view of D1) combined by the skilled person, without exercise of any inventive skills in order to solve the problem posed. The proposed solution in the independent claims thus cannot be considered inventive (Article 33(3) PCT).

What is more the use of a combination of two or more active ingredients with known identical therapeutic use can only be considered as inventive when a surprising effect, an unexpected high synergistic effect or reduced side effects for example, can be assigned in relation to the claimed therapeutic use. In this respect, the present application lacks supportive evidence.

The independent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

4) INDUSTRIAL APPLICABILITY

Present claims 1, 2, 5, 6 and 8-14 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a

known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

DE 299 24 609 U1 (PROBIODRUG AG) 22 April 2004 (2004-04-22)
WO 2004/031374 A (PROBIODRUG AG; KUEHN-WACHE, KERSTIN; BAER, JOACHIM; DEMUTH, HANS-ULRIC) 15 April 2004 (2004-04-15)